

EXHIBIT A

CLAIMS ALLOWED IN U.S. PATENT APPLICATION SERIAL NO. 09/842,289

22. A method of preparing an oral sustained release dosage form for gastrointestinal administration comprising the steps of wet granulating a mixture of xanthan gum, locust bean gum, an inert diluent and an insoluble ibuprofen in a ratio of xanthan gum to locust bean gum from about 1:20 to about 20:1 and in a ratio of the total weight of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum from about 1:0.06 to about 1:0.4; and tableting the resulting granulate into tablets containing from about 500 to about 1000 mg of said ibuprofen, said tablets providing effective blood plasma levels of said ibuprofen and a dissolution of said ibuprofen in-vitro when measured by the USP Type II (Paddle) Method, of at least about 6 percent by weight of said ibuprofen released after about 2 hours and a t_{50} at about 12 to about 16 hours.
29. The method of claim 22 wherein the ratio of ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.08 to about 1:0.25.
30. The method of claim 22 wherein said blood plasma levels are provided for a period of about 12 to about 24 hours.
31. The method of claim 22 wherein said inert diluent is selected from the group consisting of sucrose, dextrose, lactose, microcrystalline cellulose, xylitol, fructose, sorbitol, and mixtures thereof.
32. The method of claim 22, wherein said oral sustained release dosage formulation further comprises a lubricant.
33. The method of claim 22 said oral sustained release dosage formulation further comprises a wetting agent.
34. The method of claim 33, wherein said wetting agent is selected from the group consisting of polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil, polyethoxylated fatty acid from castor oil, polyethoxylated fatty acid from hydrogenated castor oil, and mixtures thereof.
35. The method of claim 33, wherein said wetting agent is included in an amount from about 5% to about 10% of the sustained release dosage formulation, by weight.
36. The method of claim 33, wherein said xanthan gum, said locust bean gum, said inert diluent, and said ibuprofen are wet granulated and then the wetting agent is added to the granulate prior to tableting.

37. The method of claim 22, further comprising a hydrophobic material.
38. The method of claim 37, wherein said hydrophobic material is selected from the group consisting of alkylcelluloses, acrylic polymers, methacrylic polymers, acrylic copolymers, methacrylic copolymers, hydrogenated vegetable oils, zein, and mixtures thereof.
39. The method of claim 38, wherein said hydrophobic material is ethylcellulose.
40. The method of claim 37, wherein said hydrophobic material is included in an amount from about 1 to about 20% by weight of the dosage formulation.
41. The method of claim 37, wherein said hydrophobic material is included in an amount from about 3 to about 12% by weight of the dosage formulation.
43. A method of preparing an oral sustained release dosage form for gastrointestinal administration comprising the steps of wet granulating a mixture of xanthan gum, locust bean gum, and an inert diluent to form an excipient, and then adding insoluble ibuprofen to said excipient, wherein a ratio of xanthan gum to locust bean gum is from about 1:20 to about 20:1 and a ratio of total weight of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4; and tableting the resulting granulate into tablets containing from about 500 to about 1000 mg of said ibuprofen, said tablets providing effective blood plasma levels of said ibuprofen and a dissolution of said ibuprofen in-vitro when measured by the USP Type II (Paddle) Method, of at least about 6 percent by weight of said ibuprofen released after about 2 hours and a t_{50} at about 12 to about 16 hours.
44. The method of claim 43, further comprising adding a wetting agent in an amount from about 5% to about 10% of the sustained release dosage formulation, by weight to the mixture of said excipient and said ibuprofen.
45. A method of preparing an oral sustained release dosage form for gastrointestinal administration comprising the steps of wet granulating a mixture of xanthan gum, locust bean gum, an inert diluent, and a hydrophobic material to form an excipient, and then adding insoluble ibuprofen to said excipient, wherein a ratio of xanthan gum to locust bean gum is from about 1:20 to about 20:1 and a ratio of the total weight of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4; and tableting the resulting granulate into tablets containing from about 500 to about 1000 mg of said ibuprofen, said tablets providing effective blood plasma levels of said ibuprofen and a dissolution of said ibuprofen in-vitro when measured by the USP Type II (Paddle) Method, of at least about

6 percent by weight of said ibuprofen released after about 2 hours and a t_{50} at about 12 to about 16 hours.

46. The method of claim 45, wherein said hydrophobic material is selected from the group consisting of alkylcelluloses, acrylic polymers, methacrylic polymers, acrylic copolymers, methacrylic copolymers, hydrogenated vegetable oils, zein, and mixtures thereof.
47. The method of claim 45, wherein said hydrophobic material is included in an amount from about 1 to about 20% by weight of the dosage formulation.
48. The method of claim 22, wherein said xanthan gum, said locust bean gum and said inert diluent are wet granulated to form an excipient and then said ibuprofen is wet granulated with said excipient prior to tableting.
49. The method of claim 37, wherein said xanthan gum, said locust bean gum, said inert diluent, and said hydrophobic material are wet granulated to form an excipient and then said ibuprofen is wet granulated with the excipient prior to tableting.

CLAIMS ALLOWED IN U.S. PATENT APPLICATION SERIAL NO. 09/654,691

93. A sustained release oral solid dosage form for providing an effective dose of a medicament having a solubility of less than about 10 g/l over a 24 hour period, comprising
an effective amount of a medicament to render a therapeutic effect;
a gelling agent comprising xanthan gum and locust bean gum in a ratio from about 1:3 to about 3:1;
a pharmaceutically acceptable cationic cross-linking agent capable of cross-linking with said gelling agent and increasing the gel strength when the dosage form is exposed to an environmental fluid; and
an inert pharmaceutical diluent, the ratio of said inert diluent to the total amount of said xanthan gum and said locust bean gum being from about 1:8 to about 8:1;
wherein said dosage form is a tablet.
96. The dosage form of claim 93, wherein a hydrophobic material selected from the group consisting of an alkylcellulose, a hydrophobic cellulosic material, a copolymer of acrylic and methacrylic acid esters, hydrogenated vegetable oils, shellac, waxes, zein and mixtures of any of the foregoing is admixed with the medicament, the xanthan and locust bean gum, the inert diluent and the cationic cross-linking agent.
97. The dosage form of claim 93, wherein said medicament is selected from the group consisting of nifedipine, nimodipine, nivadipine, nitrendipine, nisolidipine, niludipine, nicardipine and felodipine.
98. The dosage form of claim 93, wherein said medicament is nifedipine.
99. The dosage form of claim 98, wherein the amount of nifedipine is 20 mg, 30 mg, 60 mg or 90 mg.
100. The dosage form of claim 93, wherein said cationic cross-linking agent comprises an alkali metal or an alkaline earth metal sulfate, chloride, borate, bromide, citrate, acetate, or lactate.
101. The dosage form of claim 93, wherein said cationic cross-linking agent comprises calcium sulfate.
102. The sustained release oral solid dosage form of claim 93, wherein said medicament is a dihydropyridine.
103. A sustained release oral solid dosage form for providing an effective dose of a

medicament having a solubility of less than about 10 g/l over a 24 hour period, comprising
an effective amount of a medicament to render a therapeutic effect;
a gelling agent comprising xanthan gum and locust bean gum in a ratio from about 1:3 to about 3:1;
a pharmaceutically acceptable cationic cross-linking agent capable of cross-linking with said gelling agent and increasing the gel strength when the dosage form is exposed to an environmental fluid; and
an inert pharmaceutical diluent, the ratio of said inert diluent to the total amount of said xanthan gum and said locust bean gum being from about 1:8 to about 8:1;
wherein said dosage form is a tablet coated with a hydrophobic coating to a weight gain from about 1 to about 20 percent of the total weight of said tablet.

104. The sustained release oral solid dosage form of claim 103, wherein a hydrophobic material selected from the group consisting of an alkylcellulose, a hydrophobic cellulosic material, a copolymer of acrylic and methacrylic acid esters, hydrogenated vegetable oils, shellac, waxes, zein and mixtures of any of the foregoing is admixed with the medicament, the xanthan gum and locust bean gum, the inert diluent and the cationic cross-linking agent.
105. The sustained release oral solid dosage form of claim 103, wherein said medicament is a dihydropyridine.
106. The sustained release oral solid dosage form of claim 103, wherein said medicament is selected from the group consisting of nifedipine, nimodipine, nivadipine, nitrendipine, nisolidipine, niludipine, nicardipine and felodipine.
107. The sustained release oral solid dosage form of claim 103, wherein said medicament is nifedipine.
108. The sustained release oral solid dosage form of claim 107, wherein the amount of nifedipine is 20 mg, 30 mg, 60 mg, or 90 mg.
109. The sustained release oral solid dosage form of claim 103, wherein said cationic cross-linking agent comprises an alkali metal or an alkaline earth metal sulfate, chloride, borate, bromide, citrate, acetate, or lactate.
110. The sustained release oral solid dosage form of claim 103, wherein said cationic cross-linking agent comprises calcium sulfate.

Allowed Claims

Serial No. 09/879,296 Entitled **Sustained Release Heterodisperse Hydrogel Systems-Amorphous Drugs**, inventor Anand R. BAICHWAL, filed June 12, 2001. DDK 540.91195CP4

1. A method of preparing a bioavailable sustained release oral dosage form comprising combining (i) a medicament in amorphous form, (ii) a wetting agent and (iii) a sustained release excipient to obtain a mixture;
said sustained release excipient comprising a gelling agent, an ionizable gel strength enhancing agent, ethylcellulose, and an inert diluent, the ratio of inert diluent to gelling agent being from about 1:8 to about 8:1, said ionizable gel strength enhancing agent increasing the gel strength of a gel formed when said solid dosage form is exposed to an aqueous solution, said gelling agent comprising xanthan gum and locust bean gum in a ratio of said xanthan gum to said locust bean gum of from about 1:3 to about 3:1;
thereafter drying and milling said mixture to obtain a sustained release product; and
then forming said sustained release product into an oral dosage form.
2. The method of claim 1, wherein the medicament has an aqueous solubility of less than 10g/liter.
3. The method of claim 1, wherein the wetting agent is polyethylene glycol.
4. The method of claim 1, wherein said medicament is selected from the group consisting of nifedipine, nimodipine, nivadipine, nitrendipine, nisolidipine, niludipine, nicardipine and felodipine.
5. The method of claim 4 wherein said medicament is nifedipine.
6. The method of claim 3, wherein the polyethylene glycol is mixed with water to form a polyethylene glycol-water slurry prior to its being combined with the medicament and the sustained release excipient.
7. The method of claim 1, wherein said gelling agent, ionizable gel strength enhancing agent, ethylcellulose and inert diluent are premanufactured as a sustained release excipient.
8. The method of claim 1, further comprising dissolving the medicament in the wetting agent and then adding the sustained release excipient to the medicament and wetting agent.
13. The method of claim 1, wherein said gelling agent further comprises an agent selected from the group consisting of alginates, carrageenan, pectin, guar gum, xanthan gum, locust bean gum, modified starch, a cellulosic material, and mixtures of any of the foregoing.
14. The method of claim 13, wherein said cellulosic material is selected from the group consisting of hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose and hydroxypropyl cellulose and mixtures of any of the foregoing.

15. The method of claim 1 wherein said ionizable gel strength enhancing agent is selected from the group consisting of monovalent, divalent and multivalent organic or inorganic salts and mixtures thereof.
16. The method of claim 1, wherein said ionizable gel strength enhancing agent is selected from the group consisting of an alkali metal sulfate, alkali metal chloride, alkali metal borate, alkali metal bromide, alkali metal citrate, alkali metal acetate, alkali metal lactate, alkaline earth metal sulfate, alkaline earth metal chloride, alkaline earth metal borate, alkaline earth metal bromide, alkaline earth metal citrate, alkaline earth metal acetate, alkaline earth metal lactate and mixtures thereof.
17. The method of claim 1, wherein said composition further comprises an amount of a pharmaceutically acceptable hydrophobic material effective to slow the hydration of the gelling agent when said solid dosage form is exposed to gastrointestinal fluid.
18. A method of treating a patient comprising administering a dosage form prepared according to claim 1 to a patient in need of hypertensive treatment.
19. The method of claim 1, wherein the wetting agent comprises a pharmaceutically acceptable solid wetting agent.
20. The method of claim 19, wherein the wetting agent is a mixed surfactant/wetting agent system.
21. The method of claim 20, wherein the mixed surfactant/wetting agent system is selected from the group consisting of sodium lauryl sulfate/solid polyethylene glycol (PEG) 6000 and sodium lauryl sulfate/solid PEG 6000/stearic acid.
22. The method of claim 1, wherein the oral dosage form is coated with a hydrophobic polymer to a weight gain from about 1% to about 20%, by weight.
23. The method of claim 22, wherein the oral dosage form is coated with an enteric coating material in addition to the hydrophobic coating.
24. The method of claim 1, wherein the oral dosage form is coated with an enteric coating material.
25. The method of claim 24, wherein the enteric coating material is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing.
26. The method of claim 1, wherein the oral dosage form is coated with a hydrophilic coating.
27. The method of claim 22, wherein the oral dosage form is coated with a hydrophilic coating in addition to the hydrophobic coating.

28. The method of claim 24, wherein the oral dosage form is coated with a hydrophilic coating in addition to the enteric coating

29. The method of claim 23, wherein the oral dosage form is coated with a hydrophilic coating in addition to the hydrophobic coating and enteric coating.

30. A bioavailable sustained release oral solid dosage form comprising compressed agglomerated particles comprising a medicament in amorphous form having an aqueous solubility of less than about 10 g/l, a gelling agent comprising xanthan gum and locust bean gum in a ratio from about 1:3 to about 3:1, an ionizable gel strength enhancing agent, a hydrophobic material in an effective amount to slow the hydration of the gelling agent when said dosage form is exposed to gastrointestinal fluid, and an inert diluent, the ratio of inert diluent to gelling agent being from about 1:8 to about 8:1, wherein said medicament is suspended or dissolved in a pharmaceutically acceptable wetting agent prior to incorporation with the remaining ingredients of said dosage form, and wherein the amorphous form of said medicament affects the bioavailability of said oral dosage form.

31. The bioavailable sustained release oral solid dosage form of claim 30, wherein said hydrophobic material is ethylcellulose.

32. A method of treating a patient comprising administering a dosage form of claim 30 to said patient to achieve a therapeutic effective blood level of said medicament for about 12 to about 24 hours after administration.

33. The bioavailable sustained release oral dosage form of claim 30, wherein said medicament is selected from the group consisting of nifedipine, nimodipine, nivadipine, nitrendipine, nisolidipine, niludipine, nicardipine and felodipine.

34. The method of claim 30, wherein said medicament is nifedipine.

35. A method of preparing a bioavailable sustained release oral dosage form comprising: dry blending a medicament in amorphous form and a sustained release excipient to obtain a sustained release product; said sustained release excipient comprising a gelling agent comprising xanthan gum and locust bean gum in a ratio of said xanthan gum to said locust bean gum of from about 1:3 to about 3:1, an ionizable gel strength enhancing agent which increases the gel strength of a gel formed when said solid dosage form is exposed to an aqueous solution, ethylcellulose; and an inert diluent, the ratio of inert diluent to gelling agent being from about 1:8 to about 8:1; and forming said sustained release product into an oral dosage form.

36. The method of claim 35, further comprising admixing a wetting agent with the dry blended mixture of medicament, gelling agent, ionizable gel strength enhancing agent, ethylcellulose and inert diluent to form a wetting agent-based slurry, and then drying and milling the wetting agent-based slurry.

37. The method of claim 36, wherein said gelling agent, ionizable gel strength enhancing agent, ethylcellulose and inert diluent are precombined as a sustained release excipient.

38. The sustained release dosage form of claim 30, wherein said dosage form is coated with an enteric or hydrophobic polymer.

39. The sustained release dosage form of claim 30, wherein said dosage form is coated with a hydrophilic coating.

40. The sustained release dosage form of claim 30, wherein said agglomerated particles is coated with a hydrophobic polymer to a weight gain from about 1 to about 20 percent, by weight.

41. The method of claim 35, wherein the sustained release oral solid dosage form is coated with a hydrophobic polymer to a weight gain from about 1% to about 20%, by weight.

42. The method of claim 35, wherein the oral dosage form is coated with a hydrophobic polymer to a weight gain from about 1% to about 20%, by weight.

43. The method of claim 42, wherein the oral dosage form is coated with an enteric coating material in addition to the hydrophobic coating.

44. The method of claim 35, wherein the oral dosage form is coated with an enteric coating material.

45. The method of claim 44, wherein the enteric coating material is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing.

46. The method of claim 45, wherein the oral dosage form is coated with a hydrophilic coating.

47. The method of claim 42, wherein the oral dosage form is coated with a hydrophilic coating in addition to the hydrophobic coating.

48. The method of claim 44, wherein the oral dosage form is coated with a hydrophilic coating in addition to the enteric coating

49. The method of claim 43, wherein the oral dosage form is coated with a hydrophilic coating in addition to the hydrophobic coating and enteric coating.